# Reconfigurable System for Polymer-Encapsulated Nanoparticle Production

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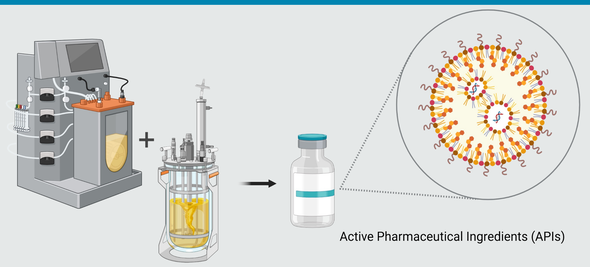
## Introduction




The processes used to produce active pharmaceutical ingredients (APIs) have traditionally been done using batch operations to maintain flexibility and quality. As biochemistry has advanced, drugs have been designed to be more potent, provoking recent technological advancements [1]. This enabled the development of modular and reconfigurable plants to produce pharmaceutical products on-demand. Utilizing nanotechnology in the pharmaceutical industry has played a significant role in the advancement of drug formulations. Nanotechnology allows site-specific and target-oriented delivery of precise medicines [2].

**Project Objective:** Design a modular and reconfigurable plant to produce polymer-encapsulated nanoparticles containing APIs. This final process design is anticipated to be an energy efficient small-scale production plant which would be capable of meeting rapidly changing market demands.

## Design Objectives

**Overall system objective: To design a modular and reconfigurable continuous plant to produce polymer-encapsulated nanoparticles ranging from 25 to 100 nm.**

| Mixer | Reactor | Polymer Encapsulation | Economic Analyses | Safety Analyses |
|---|---|---|---|---|
| Select a mixer and method to produce nanoparticles of a consistent size and uniformity to allow the finished product to function as intended. | Select a reactor that can be utilized as the second mixing device and the initial polymer encapsulation step, with the aim of producing nanoparticle clumps. | The polymer encapsulated-nanoparticle product must be consistent in both size and shape ranging from 200 to 400 nm from literature review of equipment specifications. | The plant must be able to produce finished product which can be sold at a price point consistent with non-encapsulated nanoparticle form of the API. | The finished drug product must meet the required standards under the Food and Drugs Act (FDA) and Good Manufacturing Practise (GMP) Guides. |

The scope of the design is to include preliminary preparation steps, a continuous precipitation step which uses a mixer to produce nanoparticles, a step to encapsulate the nanoparticles inside a polymer shell, and downstream processes to stabilize the particles.

## Design Overview

**Main Design Components**

**1 — Literature Review**

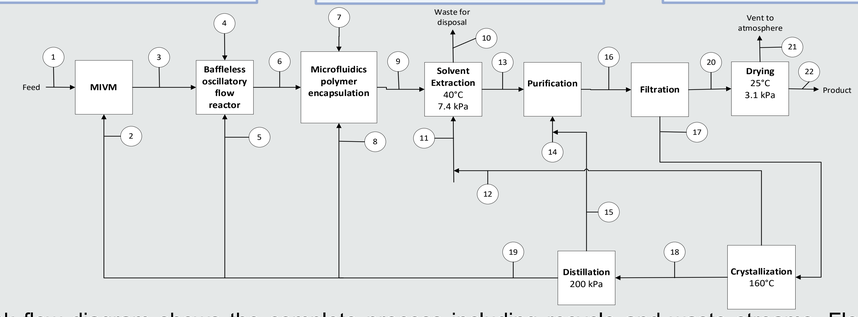
The API selected for the final plant design was acetaminophen. However, the plant was designed to be reconfigurable in terms of the variety of drugs which can be produced. By changing the chemicals used in the system other varieties of drugs can be produced as nanoparticles.

**2 — Nanoparticle Formation and Encapsulation**

The identified technologies included an MIVM for the nanoparticle formation stage, a Baffleless Ossicilating Flow Reactor (OFR) to apply the initial polymer coat and a microfluidics polymer encapsulation system to apply the second polymer coat.

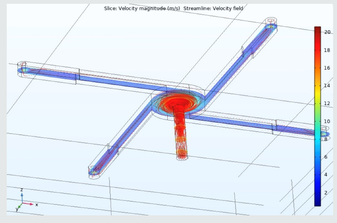
**3 — Solvent Extraction and Purification**

A solvent extraction unit, mixer for purification, filtration, and drying processes were selected to allow for removal of all solvents utilized in the nanoparticle formation. A continuous crystallizer and distillation column were also selected to allow for solvent recycle within the system.

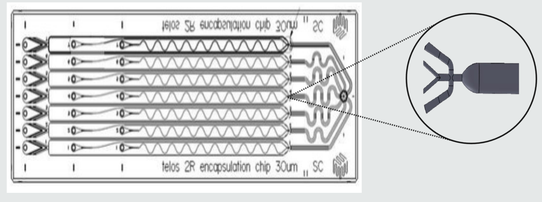



The block flow diagram shows the complete process including recycle and waste streams. Flow streams are numbered, but the stream table was excluded for simplicity.

## Design Components



The MIVM contains four inlet streams including acetaminophen mixed with a solvent, a stabilizer, also known as a block copolymer, and an anti-solvent [3]. The ratio of the streams is dependent on the desired concentration. When rapidly mixed, the stabilizer adsorbs onto the acetaminophen [3]. Nanoparticles produced by the MIVM are inputted into the baffleless oscillating flow reactor with a polymer and water to form clumps.

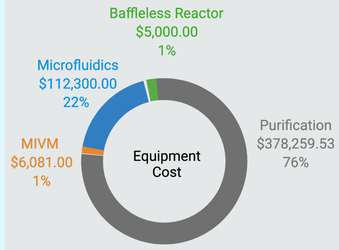


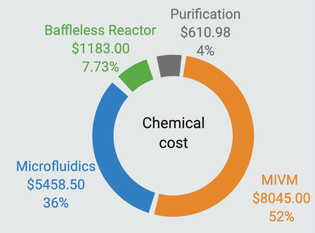
The microfluidics polymer encapsulation system contains two inlet streams. The streams contain the API clumps, the polymer and solvent mixture. The system was selected due to its high level of control over the final API nanoparticle polymer shell size and polydispersity. A hydrophilic chip with a channel size of 30 µm was selected to produce a polymer encapsulated API nanoparticle ranging in size from 200 – 400 nm.

## Safety & Economic Analyses

Safety was evaluated for both the chemicals utilized and the overall process to ensure the plant's design objectives were met. Chemical safety ensures the chemicals utilized in the production of API nanoparticles are safe for use in pharmaceutical products and consumer consumption. Process safety included performing an in-depth HAZOP analysis to mitigate any presented hazards in the plant.

Economic analysis was performed to evaluate the total equipment and chemical costs utilized in the final plant design.




## Conclusion & Recommendations

**Conclusions:**

1. Design requirments were met by the final design. The facility has continuous production, with the exception of the dryer where the particles will be inputted manually by the operator.
2. The plant's production output is approximately 1 tonne of polymer encapsulated nanoparticles per month depending on the number of operation.
3. The plant is reconfigurable as it can produce other nanoparticle products which are compatible with the selected chemicals and process equipment.

**Recommendations:**

1. Investigate the feasibility of parallel units to increase product production to allow production throughout maintenance and cleaning periods.
2. Complete further simulatory and laboratory testing to verify the particle size and concentration produced by the MIVM. Practical limitations, such as allowable viscosity, should also be determined.
3. Complete testing on the baffleless oscillatory flow reactor to determine residence times and particle clump size ranges formed.

- [1] Nusim, S. (2009). Active Pharmaceutical Ingredients: Development, Manufacturing, and Regulation, Second Edition. Taylor & Francis Group, [2] Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V., Rodriguez-Torres, M. P., Acosta-Torres, L. S., Diaz-Torres, L. A., Grillo, R., Swamy, M. K., Sharma, S., Habtemariam, S., & Shin, H. (2018). Nano based drug delivery systems: recent developments and future prospects. Journal of Nanobiotechnology, 16, Article number: 71. [3] Wang, L. Z., & Prud'homme, R. K. (2020). Flash NanoPrecipitation (FNP)–Principles and Applications in Medical Imaging and Drug Delivery.